PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/56, C07J 41/00, 31/00, 13/00, 9/00, 5/00, 7/00, 3/00, 1/00 — A1

(11) International Publication Number: WO 95/04535

(43) International Publication Date: 16 February 1995 (16.02.95)

(21) International Application Number: PCT/US94/08767

(22) International Filing Date: 2 August 1994 (02.08.94)

(30) Priority Data:
08/102,767 6 August 1993 (06.08.93) US

(71) Applicant: THE CHILDREN'S MEDICAL CENTER CORPORATION [US/US]; 55 Shattuck Street, Boston, MA 02115 (US).

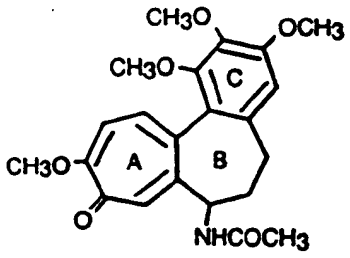
(72) Inventors: D'AMATO, Robert, John; 911 Forest Road, Lancaster, PA 17601 (US). FOLKMAN, Moses, Judah; 18 Chatham Circle, Brookline, MA 02146 (US).

(74) Agent: FREEMAN, John, W.; Fish & Richardson, 225 Franklin Street, Boston, MA 02110-2804 (US).

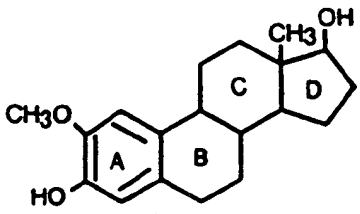
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).

Published
With international search report.

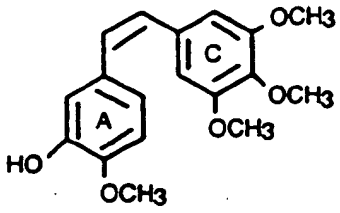
(54) Title: ESTROGENIC COMPOUNDS AS ANTI-MITOTIC AGENTS



COLCHICINE



2-METHOXYESTRADIOL



COMBRETASTATIN A-4

(57) Abstract

The application discloses methods of making medicaments for treating mammalian diseases characterized by abnormal cell mitosis by administering estradiol derivatives including those comprising colchicine or combretastatin A-4 structural motifs of general formulae found above in a dosage sufficient to inhibit cell mitosis. The application discloses novel compounds used in the methods.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

ESTROGENIC COMPOUNDS AS ANTI-MITOTIC AGENTS

Background of the Invention

This invention relates to treating disease states characterized by abnormal cell mitosis.

Cell mitosis is a multi-step process that includes cell division and replication (Alberts, B. et al. In *The Cell*, pp. 652-661 (1989); Stryer, E. *Biochemistry* (1988)). Mitosis is characterized by the intracellular movement and segregation of organelles, including mitotic spindles and chromosomes. Organelle movement and segregation are facilitated by the polymerization of the cell protein tubulin. Microtubules are formed from α and β tubulin polymerization and the hydrolysis of GTP. Microtubule formation is important for cell mitosis, cell locomotion, and the movement of highly specialized cell structures such as cilia and flagella.

Microtubules are extremely labile structures that are sensitive to a variety of chemically unrelated anti-mitotic drugs. For example, colchicine and nocadazole are anti-mitotic drugs that bind tubulin and inhibit tubulin polymerization (Stryer, E. *Biochemistry* (1988)). When used alone or in combination with other therapeutic drugs, colchicine may be used to treat cancer (WO-9303729-A, published March 4, 1993; J03240726-A, published October 28, 1991), alter neuromuscular function, change blood pressure, increase sensitivity to compounds affecting sympathetic neuron function, depress respiration, and relieve gout (*Physician's Desk Reference*, Vol. 47, p. 1487, (1993)).

Estradiol and estradiol metabolites such as 2-methoxyestradiol have been reported to inhibit cell division (Seegers, J.C. et al. *J. Steroid Biochem.* 32,

797-809 (1989); Lottering, M-L. et al. *Cancer Res.* 52, 5926-5923 (1992); Spicer, L.J. and Hammond, J.M. *Mol. and Cell. Endo.* 64, 119-126 (1989); Rao, P.N. and Engelberg, *J. Exp. Cell Res.* 48, 71-81 (1967)). However, the activity is variable and depends on a number of *in vitro* conditions. For example, estradiol inhibits cell division and tubulin polymerization in some *in vitro* settings (Spicer, L.J. and Hammond, J.M. *Mol. and Cell. Endo.* 64, 119-126 (1989); Ravindra, R., J. *Indian Sci.* 64(c) (1983)), but not in others (Lottering, M-L. et al. *Cancer Res.* 52, 5926-5923 (1992); Ravindra, R., *J. Indian Sci.* 64(c) (1983)). Estradiol metabolites such as 2-methoxyestradiol will inhibit cell division in selected *in vitro* settings depending on whether the cell culture additive phenol red is present and to what extent cells have been exposed to estrogen. (Seegers, J.C. et al. Joint NCI-IST Symposium. Biology and Therapy of Breast Cancer. 9/25-9/27, 1989, Genoa, Italy, Abstract A58).

Numerous diseases are characterized by abnormal cell mitosis. For example, uncontrolled cell mitosis is a hallmark of cancer. In addition, cell mitosis is important for the normal development of the embryo, formation of the corpus luteum, wound healing, inflammatory and immune responses, angiogenesis and angiogenesis related diseases.

Summary of the Invention

I have discovered that certain compounds within the scope of the general formulae set forth below in the claims are useful for treating mammalian diseases characterized by undesired cell mitosis. Without wishing to bind myself to any particular theory, such compounds generally inhibit microtuble formation and tubulin polymerization and/or depolymerization. Compounds within the general formulae having said inhibiting activity are preferred. Preferred compositions may also exhibit a

change (increase or decrease) in estrogen receptor binding, improved absorbtion, transport (e.g. through blood-brain barrier and cellular membranes), biological stability, or decreased toxicity. I have also discovered certain compounds useful in the method, as described by the general formulae of the claims.

A mammalian disease characterized by undesirable cell mitosis, as defined herein, includes but is not limited to excessive or abnormal stimulation of endothelial cells (e.g., atherosclerosis), solid tumors and tumor metastasis, benign tumors, for example, hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, vascular malfunctions, abnormal wound healing, inflammatory and immune disorders, Bechet's disease, gout or gouty arthritis, abnormal angiogenesis accompanying: rheumatoid arthritis, psoriasis, diabetic retinopathy, and other ocular angiogenic diseases such as retinopathy of prematurity (retrolental fibroplasic), macular degeneration, corneal graft rejection, neovascular glaucoma and Osler Weber syndrome. Other undesired angiogenesis involves normal processes including ovulation and implantation of a blastula. Accordingly, the compositions described above can be used to block ovulation and implantation of a blastula or to block menstruation (induce amenorrhea).

The bond indicated by C•••C is absent or, in combination with the C---C bond is the unit HC=CH.

Other features and advantages of the invention will be apparent from the following description of preferred embodiments thereof.

Description of the Preferred Embodiments

The drawings are first described.

Fig. 1 is a graph illustrating the inhibition of tubulin polymerization by 2-methoxyestradiol described by Example 1 below.

Fig. 2 is a graph illustrating the inhibition of colchicine binding to tubulin by 2-methoxyestradiol described by Example 2 below.

Fig. 3 depicts: I. colchicine, 2-methoxyestradiol and combretastatin A-4, and II. various estradiol derivatives comprising colchicine (a-c) or combretastatin A-4 (d) structural motifs as described below.

Compounds According to the Invention

As described below, compounds that are useful in accordance with the invention include novel estradiol derivatives that bind tubulin, inhibit microtubule formation or exhibit anti-mitotic properties. Specific compounds according to the invention are described below. Those skilled in the art will appreciate that the invention extends to other compounds within the formulae given in the claims below, having the described characteristics. These characteristics can be determined for each test compound using the assays detailed below and elsewhere in the literature.

Without wishing to bind myself to specific mechanisms or theory, it appears that certain compounds that are known to inhibit microtubule formation, bind tubulin and exhibit anti-mitotic properties such as colchicine and combretastatin A-4 share certain structural similarities with estradiol. Fig. 3 illustrates the molecular formulae of estradiol, colchicine, combretastatin A-4, and improved estradiol derivatives that bind tubulin inhibit microtubule assembly and exhibit anti-mitotic properties. Molecular formulae are drawn and oriented to emphasize structural similarities between the ring structures of colchicine, combretastatin A-4, estradiol, and certain estradiol derivatives. Estradiol derivatives are made by incorporating colchicine or combretastatin A-4 structural motifs into the steroidal backbone of estradiol.

Figure 3, part I, depicts the chemical formulae of colchicine, 2-methoxyestradiol and combretastatin A-4. Figure 3, part IIa-d, illustrates estradiol derivatives that comprise structural motifs found in colchicine or combretastatin A-4. For example, part II a-c shows estradiol derivatives with an A and/or B ring expanded from six to seven carbons as found in colchicine and part IId depicts an estradiol derivative with a partial B ring as found in combretastatin A-4. Each C ring of an estradiol derivative, including those shown in Figure 3, may be fully saturated as found in 2-methoxyestradiol. R_{1-6} represent a subset of the substitution groups found in the claims. Each $R_1 \rightarrow R_6$ can independently be defined as $-R_1$, OR_1, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I, or $-C{\equiv}CH$.

Anti-mitotic Activity *In Situ*

Anti-mitotic activity is evaluated *in situ* by testing the ability of an improved estradiol derivative to inhibit the proliferation of new blood vessel cells (angiogenesis). A suitable assay is the chick embryo chorioallantoic membrane (CAM) assay described by Crum et al. *Science* 230:1375 (1985). See also, U.S. Patent 5,001,116, hereby incorporated by reference, which describes the CAM assay. Briefly, fertilized chick embryos are removed from their shell on day 3 or 4, and a methylcellulose disc containing the drug is implanted on the chorioallantoic membrane. The embryos are examined 48 hours later and, if a clear avascular zone appears around the methylcellulose disc, the diameter of that zone is measured. Using this assay, a 100mg disk of the estradiol derivative 2-methoxyestradiol was found to inhibit cell mitosis and the growth of new blood vessels after 48 hours. This result indicates that the anti-mitotic action of 2-methoxyestradiol can inhibit cell mitosis and angiogenesis.

Anti-Mitotic Activity *In Vitro*

Anti-mitotic activity can be evaluated by testing the ability of an estradiol derivative to inhibit tubulin polymerization and microtubule assembly *in vitro*. Microtubule assembly is followed in a Gilford recording spectrophotometer (model 250 or 2400S) equipped with electronic temperature controllers. A reaction mixture (all concentrations refer to a final reaction volume of 0.25µl) contains 1.0M monosodium glutamate (ph 6.6), 1.0mg/ml (10µM) tubulin, 1.0 mM $MgCl_2$, 4% (v/v) dimethylsulfoxide and 20-75µM of a composition to be tested. The 0.24ml reaction mixtures are incubated for 15 min. at 37°C and then chilled on ice. After addition of 10µl 2.5mM GTP, the reaction mixture is transferred to a cuvette at 0°C, and a baseline established. At time zero, the temperature controller of the spectrophotometer is set at 37°C. Microtubule assembly is evaluated by increased turbity at 350 nm. Alternatively, inhibition of microtubule assembly can be followed by transmission electron microscopy as described in Example 2 below.

Indications

The invention can be used to treat any disease characterized by abnormal cell mitosis. Such diseases include, but are not limited to: abnormal stimulation of endothelial cells (e.g., atherosclerosis), solid tumors and tumor metastasis, benign tumors, for example, hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, vascular malfunctions, abnormal wound healing, inflammatory and immune disorders, Bechet's disease, gout or gouty arthritis, abnormal angiogenesis accompanying: rheumatoid arthritis, psoriasis, diabetic retinopathy, and other ocular angiogenic diseases such as retinopathy of prematurity (retrolental fibroplasic), macular degeneration, corneal

graft rejection, neuroscular glacoma and Oster Webber syndrome.

Improved Estradiol Derivative Synthesis

Known compounds that are used in accordance with the invention and precursors to novel compounds according to the invention can be purchased, e.g., from Sigma Chemical Co., St. Louis, Steroloids and Research Plus. Other compounds according to the invention can be synthesized according to known methods from publicly available precursors.

The chemical synthesis of estradiol has been described (Eder, V. et al., *Ber* 109, 2948 (1976); Oppolzer, D.A. and Roberts, D.A. *Helv. Chim. Acta.* 63, 1703, (1980)). Synthetic methods for making seven-membered rings in multi-cyclic compounds are known (Nakamuru, T. et al. *Chem. Pharm. Bull.* 10, 281 (1962); Sunagawa, G. et al. *Chem. Pharm. Bull.* 9, 81 (1961); Van Tamelen, E. E. et al. *Tetrahedran* 14, 8-34 (1961); Evans, D. E. et al. *JACS* 103, 5813 (1981)). Those skilled in the art will appreciate that the chemical synthesis of estradiol can be modified to include 7-membered rings by making appropriate changes to the starting materials, so that ring closure yields seven-membered rings. Estradiol or estradiol derivatives can be modified to include appropriate chemical side groups according to the invention by known chemical methods (*The Merck Index*, 11th Ed., Merck & Co., Inc., Rahway, NJ USA (1989), pp. 583-584).

Administration

The compositions described above can be provided as physiologically acceptable formulations using known techniques, and these formulations can be administered by standard routes. In general, the combinations may be administered by the topical, oral, rectal or parenteral (e.g., intravenous, subcutaneous or intramuscular) route.

In addition, the combinations may be incorporated into biodegradable polymers allowing for sustained release, the polymers being implanted in the vicinity of where delivery is desired, for example, at the site of a tumor. The biodegradable polymers and their use are described in detail in Brem et al., *J. Neurosurg.* 74:441-446 (1991).

The dosage of the composition will depend on the condition being treated, the particular derivative used, and other clinical factors such as weight and condition of the patient and the route of administration of the compound. However, for oral administration to humans, a dosage of 0.01 to 100 mg/kg/day, preferably 0.01-1 mg/kg/day, is generally sufficient.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intraocular, intratracheal, and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the active ingredient and the pharmaceutical carrier(s) or excipient(s). In general, the formulations are prepared by uniformly and intimately bringing into associate the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tables may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally coated or scored and may be formulated so as to provide a slow or controlled release of the active ingredient therein.

Formulations suitable for topical administration in the mouth include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier.

Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels and pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier. A preferred topical delivery system is a transdermal patch containing the ingredient to be administered.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations, wherein the

carrier is a liquid, for administration, as for example, a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such as carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) conditions requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tables of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the administered ingredient.

It should be understood that in addition to the ingredients, particularly mentioned above, the formulations of this invention may include other agents convention in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include flavoring agents.

Example 1:

Figure 1 illustrates the inhibition of tubulin polymerization by 2-methoxyestradiol.

A. Each reaction mixture (all concentrations refer to the final reaction volume of 0.25 ml) contained 1.0 M monosodium glutamate (pH 6.6), 1.0 mg/ml (10 μM) tubulin, 1.0 mM $MgCl_2$, 4% (v/v) dimethylsulfoxide, and either 0 (curve 1), 20 μM (curve 2), 40 μM (curve 3), or 75 μM (curve 4) 2-methoxyestradiol. The 0.24 ml reaction mixtures were incubated for 15 min at 37°C and chilled on ice. After addition of 10 μl of 2.5 mM GTP the reaction mixtures were transferred to cuvettes held at 0°C, and baselines were established. At time zero the temperature controller was set at 37°C. At the times indicated by the vertical dashed lines the temperature controller was set at the indicated temperatures.

B. Each reaction mixture contained 0.8 M monosodium glutamate (pH 6.6), 1.2 mg/ml (12 μM) tubulin, 4% (v/v) dimethylsulfoxide, and either 0 (curve 1), 1.0 μM (curve 2), 2.0 μM (curve 3), 3.0 μM (curve 4), or 4.0 μM (curve 5) 2-methoxyestradiol. The 0.24 ml reaction mixtures were incubated for 15 min at 26°C and chilled on ice. After addition of 10μl of 10 mM GTP the reaction mixtures were transferred to cuvettes held at 0°C, and baselines were established. At time zero the temperature controller was set at 26°C. At the time indicated by vertical dashed line the temperature controller was set at 0°C.

Example 2:

Transmission electron microscopy (TEM) can show differences between the morphology of polymerized tubulin formed in the absence or presence of 2-methoxyestradiol. After a 30 min incubation (37°C) of reaction mixtures containing the components described in Example 1, 75 μM 2-methoxyestradiol was added, and aliquots were placed on 200-mesh carbon coated copper grids and stained with 0.5% (w/v) uranyl acetate. TEM magnifications from 23,100X to 115,400X were used to visualize differences in tubulin morphology.

Example 3:

Figure 2 illustrates that 2-methoxyestradiol inhibits colchicine binding to tubulin. Reaction conditions were as described in the text, with each reaction mixture containing 1.0 μM tubulin, 5% (v/v) dimethyl sulfoxide, 5 μM [^{3}H]colchicine, and inhibitor at the indicated concentrations. Incubation was for 10 min at 37°C. Symbols as follows: o, 2-methoxyestradiol; •, combretastatin A-4; ▵, dihydrocombretastatin A-4. Combretastatin A-4 and dihydrocombretastatin A-4 are compounds with anti-mitotic activity similar to colchicine.

Example 4:

Table 1 illustrates the inhibitory effects on tubulin polymerization *in vitro* exhibited by estradiol or estradiol derivatives, plant anti-mitotic compounds such as colchicine, combretastatin A-4 or other plant compounds . The method is given in Example 1.

Example 5:

Table 2 lists estrogens, estradiol or estradiol derivatives that inhibit colchicine binding to tubulin, by the method given in Example 3.

Table 1

Estrogenic Compound	IC_{50} (μM ± S.D.)
2-Methoxyestradiol	1.9 ± 0.2
Diethylstilbestrol	2.4 ± 0.4
2-Bromoestradiol	4.5 ± 0.6
2-Methoxyestrone	8.8 ± 1
17-Ethynylestradiol	10.0 ± 2
2-Fluoroestradiol	27.0 ± 6
Estradiol	30.0 ± 6
Estrone	> 40
2-Methoxy-17-ethynylestradiol	> 40
Estriol	> 40
2-Methoxyestriol	> 40
Estradiol-3-O-methyl ether	> 40
2-Methoxyestradiol-3-O-methyl ether	> 40
4-Methoxyestradiol	> 40
4-Methoxyestradiol-3-O-methyl ether	> 40

Plant Products	IC_{50} (μM ± S.D.)
Colchicine	0.80 ± 0.07
Podophyllotoxin	0.46 ± 0.02
Combretastatin A-4	0.53 ± 0.05
Dihydrocombretastatin A-4	0.63 ± 0.03

IC_{50} values are defined as the concentration of an estradiol derivative required to inhibit tubulin polymerization by 50%. IC_{50} values were obtained in at least two independent experiments for non-inhibitory agents (IC_{50} > 40 μM) and at least three independent experiments for inhibitory compounds. IC_{50} values were obtained graphically, and average values are presented. S.D., standard deviation.

Table 2

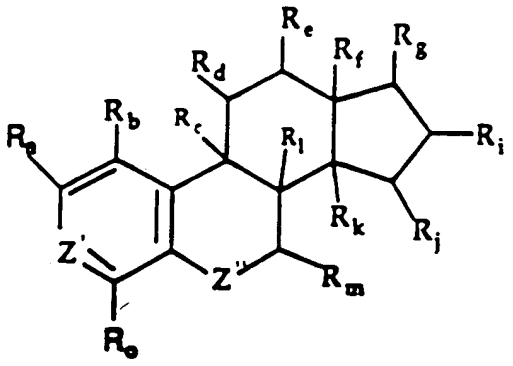
Estrogenic Compound	Percent inhibition ± S.D.
2-Methoxyestradiol	82 ± 2
2-Methoxyestrone	57 ± 6
17-Ethynylestradiol	50 ± 7
Estradiol	38 ± 4
Diethylstilbestrol	30 ± 4

Reaction conditions were described in Example 3, with each reaction mixture containing 1.0 μM tubulin, 5% (v/v) dimethyl sulfoxide, 2 μM [^{3}H]colchicine, and 100 μM inhibitor. Incubation was for 10 min at 37°C. Average values obtained in three independent experiments are presented in the table, except for 2-methoxyestrone, which was only examined twice. S.D., standard deviation.

What is claimed is:

Claims

1. A method of making a medicament which is capable of inhibiting abnormal cell mitosis, said medicament comprising, in a pharmaceutically acceptable carrier, a cell mitosis-inhibiting compound of the formula:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_d, R_e, R_f, R_i, R_j, R_k, R_l, R_m, R_o, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and R_g is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I, or $-C\equiv CH$;

or

B) each R_a, R_b, R_c, R_f, R_k, R_l, R_o, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and each R_d, R_e, R_i, R_j, R_m, independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$; and R_g is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$, or $-C\equiv CH$;

and

II. Z′ is defined as follows:

A) Z′ is X, where X is $>COR_1$, $>C\overset{O}{\overset{\|}{C}}-R_1$, $>C\overset{O}{\overset{\|}{C}}-OR_1$, $>C\overset{OH}{\overset{|}{C}}-R_1$, $>C\overset{OH}{\overset{|}{C}}-OR_1$;

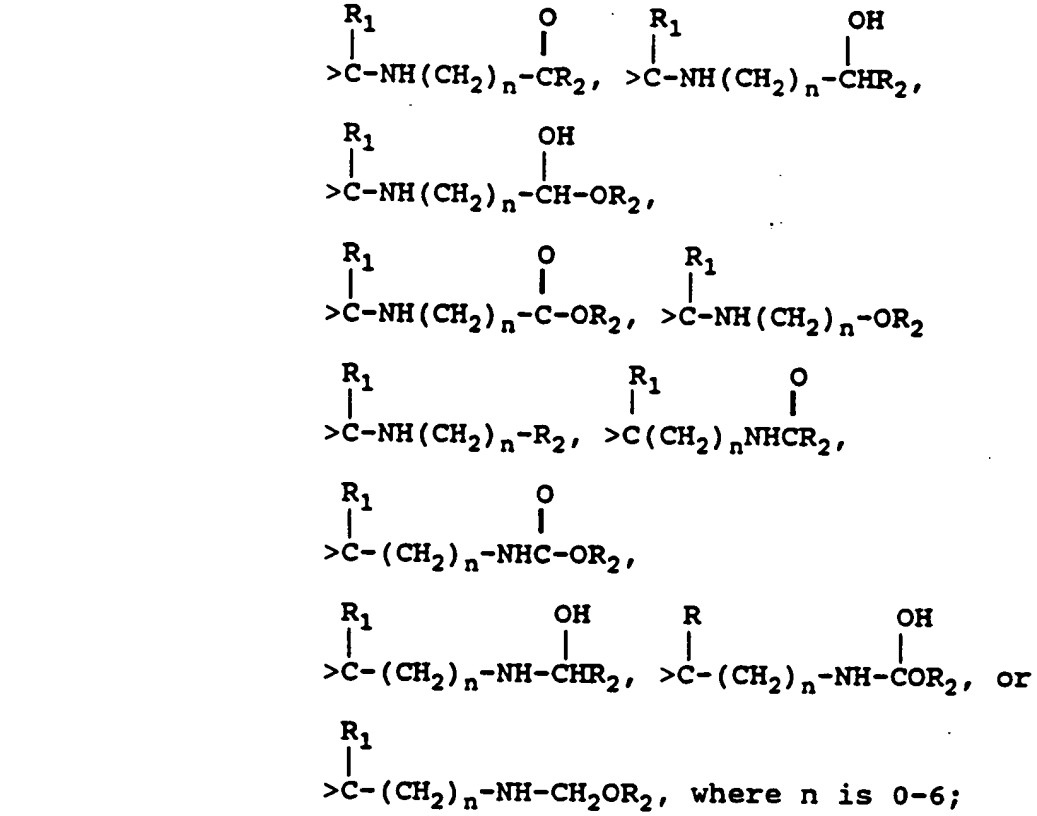
or

B) Z′ is $=C(R_n)-X'-$ or $-X'-C(R_n)=$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$; and X′ is X, as defined above; or X′ is $>C=O$;

and

III. Z" is defined as follows:

A) Z" is Y, where Y is $-O-$, $-N(R_1)-$, $>CHR_1$, $>C(R_1)-(CH_2)_nOR_2$, $>C=O$, $>C(R_1)-(CH_2)_n-CR_2$, $>C(R_1)-(CH_2)_n-C(=O)-OR_2$, $>C(R_1)-(CH_2)_n-CHR_2$, $>C(R_1)-(CH_2)_n-CH(OH)-OR_2$,



or

B) Z" is $-Y-\underset{\underset{R_p}{|}}{CH}-$ or $-\underset{\underset{R_p}{|}}{CH}-Y-$ where R_p is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$;

and

IV. provided that when each R_b, R_c, R_d, R_e, R_i, R_j, R_k, R_l, R_m and R_o is H;

R_f is $-CH_3$;

R_g is $-OH$;

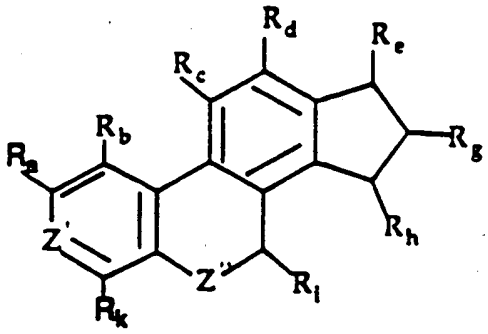
Z' is >COH; and

Z" is $>CH_2$;

then R_a is not -H;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

2. A method of making a medicament which is capable of inhibiting abnormal cell mitosis, said medicament comprising, in a pharmaceutically acceptable carrier, a cell mitosis inhibiting compound of the formula:



wherein:

I. R_a-R_k are defined as follows:

A) each R_a, R_b, R_c, R_d, R_g, R_h, R_i, R_k independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$,-F, $-NHR_2$, -Br, or -I; and R_e is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I or -C≡CH;

or

B) each R_a, R_b, R_c, R_d, R_k, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and each R_{eg}, R_h, R_i, independently is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, -Br, or -I; and R_e is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, -Br, -I or -C≡CH;

and

II. Z′ is defined as follows:

A) Z′ is X, where X is $>COR_1$, $>C(=O)-R_1$,

$>C(=O)-OR_1$, $>CH(OH)-R_1$, $>C(OH)-OR_1$;

or

B) Z′ is $=C(R_n)-X'-$ or $-X'-C(R_n)=$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$, and X′ is X, as defined above; or X′ is also $>C=O$;

and

III. Z" is defined as follows:

A) Z" is Y, where Y is $-O-$, $-N(R_1)-$, $>CHR_1$,

$>C=O$, $>C(R_1)-(CH_2)_nOR_2$,

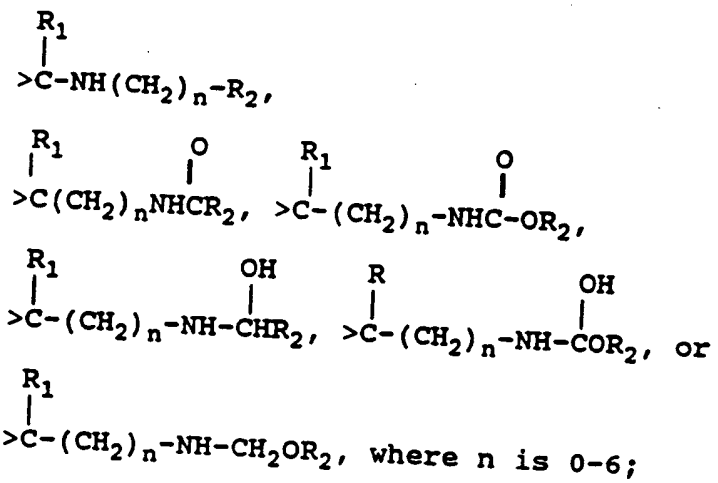
$>C(R_1)-(CH_2)_n-CR_2(=O)$, $>C(R_1)-(CH_2)_n-C(=O)-OR_2$,

$>C(R_1)-(CH_2)_n-CHR_2(OH)$, $>C(R_1)-(CH_2)_n-CH(OH)-OR_2$,

$>C(R_1)-NH(CH_2)_n-CR_2(=O)$, $>C(R_1)-NH(CH_2)_n-CHR_2(OH)$,

$>C(R_1)-NH(CH_2)_n-CH(OH)-OR_2$,

$>C(R_1)-NH(CH_2)_n-C(=O)-OR_2$, $>C(R_1)-NH(CH_2)_n-OR_2$,



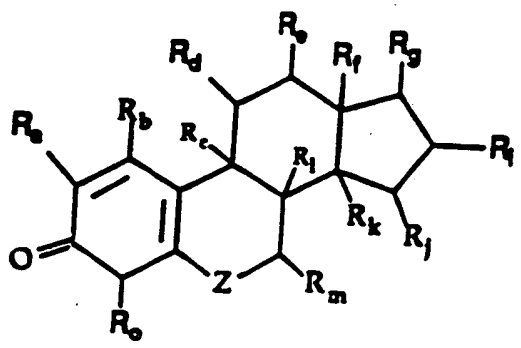
or

B) Z" is -Y-CH- or -CH-Y-, where R_p is
R_p R_p

$-R_1$, $-OR_1$, $-SR_1$, -F, $-NHR_2$, -Br or -I;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

3. A method of making a medicament which is capable of inhibiting abnormal cell mitosis, said medicament comprising, in a pharmaceutically acceptable carrier, a cell mitosis-inhibiting compound of the formula:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_d, R_e, R_f, R_i, R_j, R_k, R_l, R_m, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and R_g is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ or $-C\equiv CH$;

or

B) each R_a, R_b, R_c, R_f, R_k, R_l, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and each R_d, R_e, R_i, R_j, R_m, R_o independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and R_g is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ or $-C\equiv CH$;

and

II. Z is defined as follows:

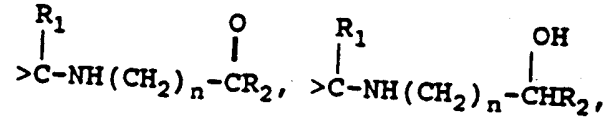
A) Z is Y, where Y is $-O-$, $-\overset{R_1}{\underset{|}{N}}-$, $>CHR_1$,

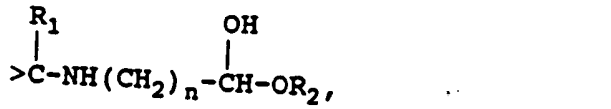
$>C=O$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_nOR_2$,

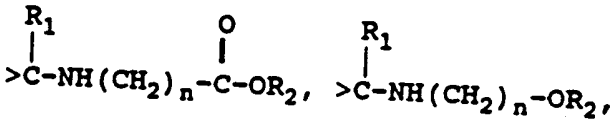
$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$,

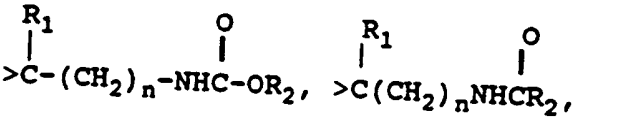
$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{CH}}-R_2$,

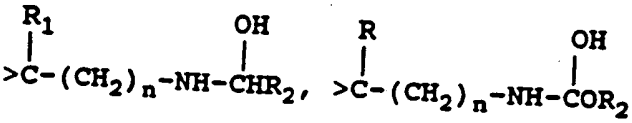
$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{CH}}-OR_2$,

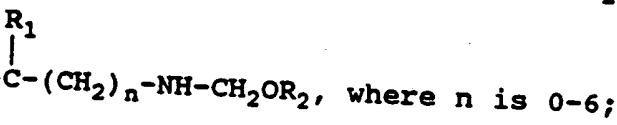




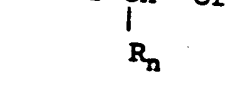






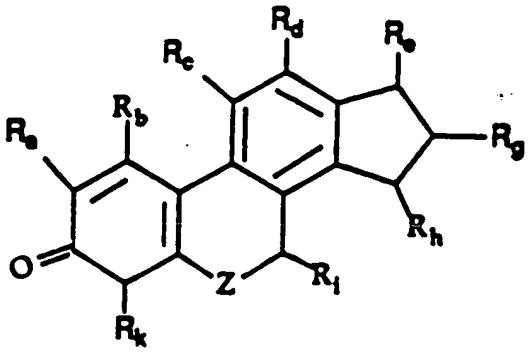


or

B) Z is  or , where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

4. A method of making a medicament which is capable of inhibiting abnormal cell mitosis, said medicament comprising, in a pharmaceutically acceptable carrier, a cell mitosis-inhibiting compound of the formula:



wherein:

I. R_a-R_k are defined as follows:

A) each R_a, R_b, R_c, R_d, R_g, R_h, R_i, R_k independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, or $-I$; and R_e is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, $-I$ or $-C\equiv CH$;

or

B) each R_a, R_b, R_c, R_d, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, or $-I$ and each R_g, R_h, R_i, R_k independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$ or $-I$; and R_e is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, $-I$ or $-C\equiv CH$;

and

II. Z is defined as follows:

A) Z is Y, where Y is -O-, $-\overset{R_1}{\underset{|}{N}}-$, $>CHR_1$,

$>C=O$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_nOR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{C}}HR_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{C}}H-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{C}}HR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{C}}H-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-R_2$, $>\overset{R_1}{\underset{|}{C}}(CH_2)_nNH\overset{O}{\overset{\|}{C}}R_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH\overset{O}{\overset{\|}{C}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH-\overset{OH}{\underset{|}{C}}HR_2$, $>\overset{R}{\underset{|}{C}}-(CH_2)_n-NH-\overset{OH}{\underset{|}{C}}OR_2$, or

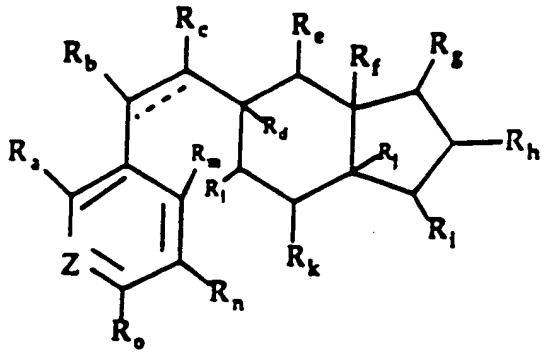
$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH-CH_2OR_2$, where n is 0-6;

or

B) Z is $-Y-\overset{R_n}{\underset{|}{C}}H-$ or $-\overset{R_n}{\underset{|}{C}}H-Y-$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, -F, $-NHR_2$, -Br or -I;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

5. A method of making a medicament which is capable of inhibiting abnormal cell mitosis, said medicament comprising, in a pharmaceutically acceptable carrier, a cell mitosis-inhibiting compound of the formula:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_d, R_e, R_f, R_g, R_h, R_j, R_k, R_l, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and R_i is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I or -C≡CH;

or

B) each R_a, R_d, R_f, R_j, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCR_1$, $-SR_1$,

$-F$, $-NHR_2$, $-Br$, or $-I$; and each R_b, R_c R_e, R_g, R_h, R_k, R_l independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$ or $-I$; and R_i is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-Br$, $-I$ or $-C\equiv CH$;

or

C) each R_a, R_b, R_c, R_d, R_f, R_j, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, OCR_1, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ and each R_e, R_g, R_h, R_k, R_l independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$ or $-I$; and R_i is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-Br$, $-I$ or $-C\equiv CH$;

II. Z is defined as follows:

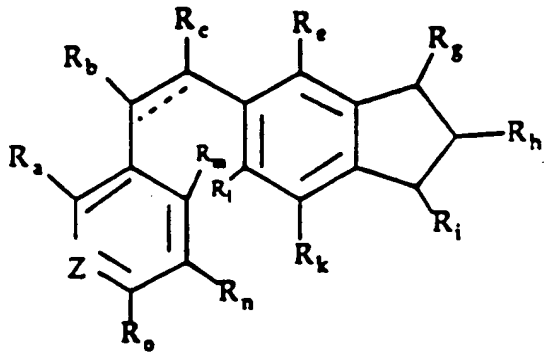
A) Z is X, where X is $>COR_1$, $>C(=O)-R_1$, $>C(=O)-OR_1$, $>C(OH)-R_1$, $>C(OH)-OR$;

or

B) Z is $=C(R_p)-X'-$ or $-X'-C(R_p)=$, where R_p is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$; and X′ is X, as defined above; or X′ is $>C=O$;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons; and the bond indicated by C•••C is absent or, in combination with the C—C bond, is the unit HC=CH.

6. A method of making a medicament which is capable of inhibiting abnormal cell mitosis, said medicament comprising, in a pharmaceutically acceptable carrier, a cell mitosis-inhibiting compound of the formula:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_e, R_g, R_h, R_k, R_l, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and R_i is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ or $-C\equiv CH$;

or

B) each R_a, R_e, R_l, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ and each R_b, R_c, R_g, R_h is $=O$,

$-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br or -I; and R_i is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br, -I or -C≡CH;

or

C) each R_a, R_b, R_c, R_e, R_k, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I, and each R_h, R_i independently is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br or -I; and R_i is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br, -I or -C≡CH;

and

I. Z is defined as follows:

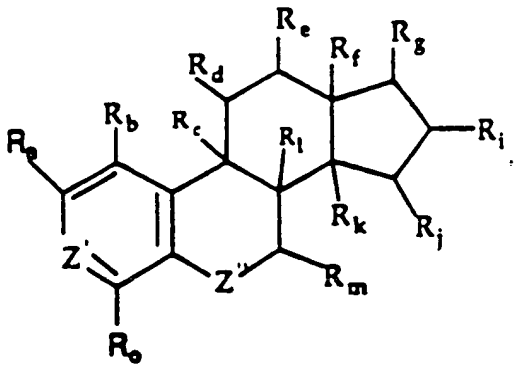
A) Z is X, where X is $>COR_1$, $>CC(=O)-R_1$, $>CC(=O)-OR_1$, $>CC(OH)-R_1$, $>CC(OH)-OR$;

or

B) Z is $=C(R_p)-X'-$ or $-X'-C(R_p)=$, where R_p is $-R_1$, $-OR_1$, $-SR_1$, -F, $-NHR_2$, -Br or -I, and X′ is X, as defined above; or X′ is =O;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons; and the bond indicated by C•••C is absent or, in combination with the C—C bond is the unit HC=CH.

7. A compound of the general formula below, said compound being a cell-mitosis-inhibiting compound:



wherein:

I. R_a-R_o are defined as follows:

(A) each R_a, R_b, R_c, R_d, R_e, R_f, R_i, R_j, R_k, R_l, R_m, R_o, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$,-Br, or -I; and R_g is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I or -C≡CH;

or

(B) each R_a, R_b, R_c, R_f, R_k, R_l, R_o, is $-R_1$, $-OR_1$, $-OCOR_1$ $-SR_1$, -F, $-NHR_2$, -Br, or -I; and each R_d, R_e, R_i, R_j, R_m, independently is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F,$-NHR_2$, -Br or -I; and R_g is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I or -C≡CH;

and

II. Z′ is defined as follows:

A) Z′ is X, where X is $>COR_1$, $>C(=O)-R_1$,

$>C(=O)-OR_1$, $>C(OH)-R_1$, $>C(OH)-OR_1$;

or

B) Z′ is $=C(R_n)-X'-$ or $-X'-C(R_n)=$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$; or X′ is X, as defined above; or X′ is $>C=O$;

and

III. Z" is defined as follows:

A) Z" is Y, where Y is $-O-$, $-N(R_1)-$, $>CHR_1$,

$>C=O$, $>C(R_1)-(CH_2)_nOR_2$,

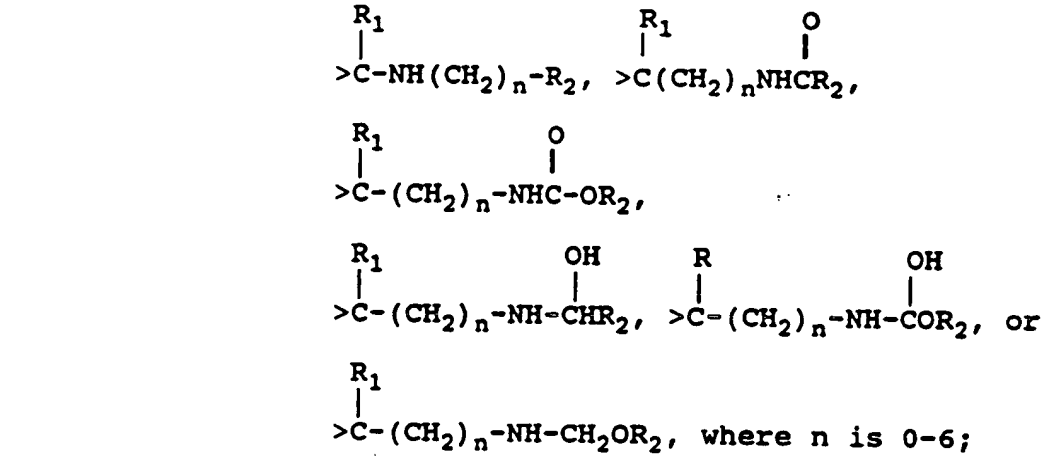
$>C(R_1)-(CH_2)_n-CR_2$, $>C(R_1)-(CH_2)_n-C(=O)-OR_2$,

$>C(R_1)-(CH_2)_n-CHR_2$, $>C(R_1)-(CH_2)_n-CH(OH)-OR_2$,

$>C(R_1)-NH(CH_2)_n-CR_2$, $>C(R_1)-NH(CH_2)_n-CHR_2$,

$>C(R_1)-NH(CH_2)_n-CH(OH)-OR_2$,

$>C(R_1)-NH(CH_2)_n-C(=O)-OR_2$, $>C(R_1)-NH(CH_2)_n-OR_2$



or

B) Z" is -Y-CH- or -CH-Y- where R_p is $-R_1$, $-OR_1$, $-SR_1$, -F, $-NHR_2$, -Br or -I;

provided that when:

3) each R_b, R_c, R_d, R_e, R_j R_k, R_l, R_m, is -H;

R_f is $-CH_3$;

R_g is -OH, $-OCCH_3$;

R_i is -H, -OH, or =O;

R_o is -H or -Br;

Z' is >COH; and

Z" is $>CH_2$ or -OH; then

R_a is not -F, -Br, -OH or -H;

and

4) each R_b, R_c, R_d, R_e, R_i, R_j R_k, R_l, R_m, is -H;

R_f is $-CH_3$;

R_g is -OH; and

Z" is $>CH_2$; then

Z' is not $>COCH_3$ or $>C(=O)CH_3$; and
each R_a, R_o independently or together
are not $-OCH_3$ or -H;

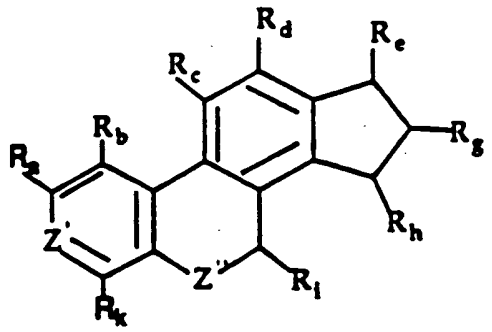
and

5) each R_c, R_e, R_j, R_k, R_l, R_m, R_o is -H;
R_a is -H or $-OCH_3$;
R_b is -H or $-CH_3$;
R_d is -OH;
R_f is $-CH_3$;
R_g is =O;
R_i is -OH, =O or $-C\equiv CH$; and
Z" is $>CH_2$; then

Z' is not >COH; $>C(=O)CH_3$, or -H;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

8. A compound of the general formula below, said compound being a cell-mitosis-inhibiting compound:



wherein:

I. R_a-R_k are defined as follows:

A) each R_a, R_b, R_c, R_d, R_g, R_h, R_i, R_k independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and R_e is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ or $-C\equiv CH$;

or

B) each R_a, R_b, R_c, R_d, R_k, is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and each R_g, R_h, R_i, independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-Br$, or $-I$; and R_e is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-Br$, $-I$ or $-C\equiv CH$;

and

I. Z′ is defined as follows:

A) Z′ is X, where X is $>COR_1$, $>C_2C(=O)-R_1$,

$>C_2C(=O)-OR_1$, $>CC(OH)-R_1$, $>C(OH)-C-OR_1$;

or

B) Z′ is $=C(R_n)-X'-$ or $-X'-C(R_n)=$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$, and X′ is X, as defined above; or X′ is also $>C=O$;

and

II. Z" is defined as follows:

A) Z" is Y, where Y is -O-, $-\overset{R_1}{\underset{|}{N}}-$, $>CHR_1$,

$>C=O$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_nOR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{C}}HR_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{C}}H-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{C}}HR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{C}}H-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-R_2$,

$>\overset{R_1}{\underset{|}{C}}(CH_2)_nNH\overset{O}{\overset{\|}{C}}R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH\overset{O}{\overset{\|}{C}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH-\overset{OH}{\underset{|}{C}}HR_2$, $>\overset{R}{\underset{|}{C}}-(CH_2)_n-NH-\overset{OH}{\underset{|}{C}}OR_2$, or

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH-CH_2OR_2$, where n is 0-6;

or

B) Z" is $-Y-\overset{R_p}{\underset{|}{C}}H-$ or $-\overset{R_p}{\underset{|}{C}}H-Y-$, where R_p is

$-R_1$, $-OR_1$, $-SR_1$, -F, $-NHR_2$, -Br or -I;

$-F$, $-NHR_1$, $-Br$, or $-I$; and R_e is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, $-I$ or $-C\equiv CH$;

or

B) each R_a, R_b, R_c, R_d, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, or $-I$; and each R_g, R_h, R_i, R_k independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$ or $-I$; and R_e is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, $-I$ or $-C\equiv CH$;

II. Z is defined as follows:

1) Z is Y, where Y is $-O-$, $-\overset{R_1}{\underset{|}{N}}-$, $>CHR_1$,

$>C=O$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_nOR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{CH}}R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{CH}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{CH}}R_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{CH}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-R_2$, $>\overset{R_1}{\underset{|}{C}}(CH_2)_nNH\overset{O}{\overset{\|}{C}}R_2$

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH\overset{O}{\overset{\|}{C}}-OR_2$,

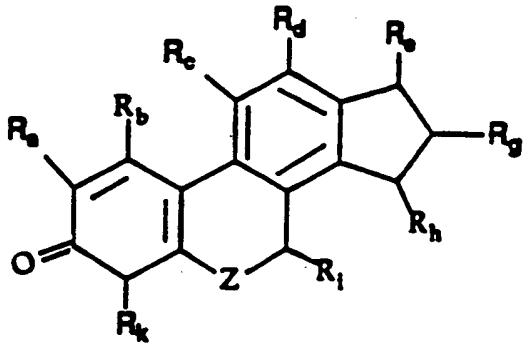
$>C(R_1)-(CH_2)_n-NH-CHR_2OH$, $>C(R)-(CH_2)_n-NH-COR_2OH$, or $>C(R_1)-(CH_2)_n-NH-CH_2OR_2$, where n is 0-6;

or

B) Z is $-Y-CH(R_n)-$ or $-CH(R_n)-Y-$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

10. A compound of the general formula below, said compound being a cell-mitosis-inhibiting compound:



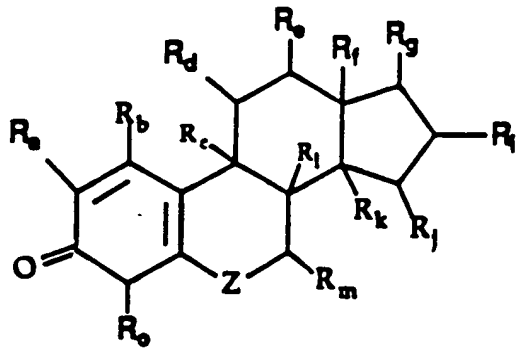
wherein:

I. R_a-R_k are defined as follows:

A) each R_a, R_b, R_c, R_d, R_g, R_h, R_i, R_k independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$,

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

9. A compound of the general formula below, said compound being a cell-mitosis-inhibiting compound:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_d, R_e, R_f, R_i, R_j, R_k, R_l, R_m, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and R_g is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I or -C≡CH;

or

B) each R_a, R_b, R_c, R_f, R_k, R_l, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and each R_d, R_e, R_i, R_j, R_m, R_o independently is =O, $-R_1$, $-OR_1$, $-OCOR_1$,

$-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$; and R_g is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ or $-C\equiv CH$;

and

II. Z is defined as follows:

A) Z is Y, where Y is $-O-$, $-\overset{R_1}{\underset{|}{N}}-$, $>CHR_1$,

$>C=O$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_nOR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{C}}HR_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-\overset{OH}{\underset{|}{C}}H-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-R_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{C}}HR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{OH}{\underset{|}{C}}H-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-\overset{O}{\overset{\|}{C}}-OR_2$, $>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-OR_2$,

$>\overset{R_1}{\underset{|}{C}}-NH(CH_2)_n-R_2$,

$>\overset{R_1}{\underset{|}{C}}-(CH_2)_n-NH\overset{O}{\overset{\|}{C}}-OR_2$, $>\overset{R_1}{\underset{|}{C}}(CH_2)_nNH\overset{O}{\overset{\|}{C}}R_2$,

$>C(R_1)-(CH_2)_n-NH-CH(OH)R_2$, $>C(R)-(CH_2)_n-NH-C(OH)R_2$, or

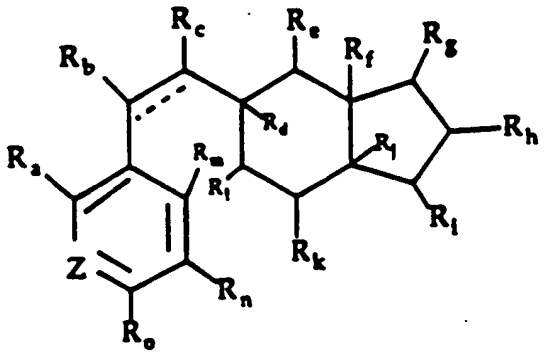
$>C(R_1)-(CH_2)_n-NH-CH_2OR_2$, where n is 0-6;

or

Z is $-Y-CH(R_n)-$ or $-CH(R_n)-Y-$, where R_n is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons.

11. A compound of the general formula below, said compound being a cell-mitosis-inhibiting compound:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_d, R_e, R_f, R_g, R_h, R_j, R_k, R_l, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and R_i is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I or -C≡CH;

or

B) each R_a, R_d, R_f, R_j, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCR_1$, $-SR_1$, -F, $-NHR_2$, -Br, -I; and each R_b, R_c, R_e, R_g, R_h, R_k, R_l independently is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br or -I; and R_i is =0, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br, -I or -C≡CH;

or

C) each R_a, R_b, R_c, R_d, R_f, R_j, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, OCR_1, $-SR_1$, -F, $-NHR_2$, -Br, -I; and each R_e, R_g, R_h, R_k, R_l independently is =O, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br or -I; and R_i is =0, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_1$, -Br, -I or -C≡CH;

and

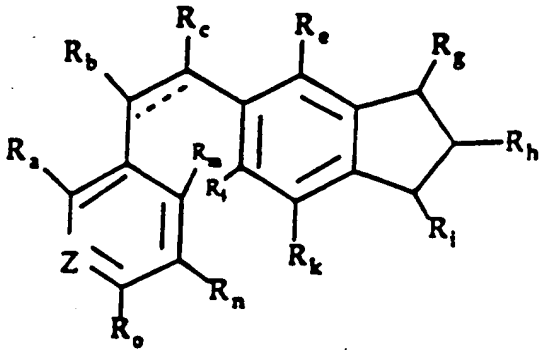
I. Z is defined as follows:

1) Z is X, where X is $>COR_1$, $>C(=O)-R_1$, $>C(=O)-OR_1$, $>C(OH)-R_1$, $>C(OH)-OR$; or

Z is $=C(R_p)-X'-$ or $-X'-C(R_p)=$, where R_p is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$; and X′ is X, as defined above; or X′ is >C=O;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons; and the bond indicated by C•••C is absent or, in combination with the C—C bond is the unit HC=CH.

12. A compound of the general formula below, said compound being a cell-mitosis-inhibiting compound:



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_e, R_g, R_h, R_k, R_l, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, or $-I$; and R_i is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$ or $-C\equiv CH$;

or

B) each R_a, R_e, R_l, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$; and each R_b, R_c, R_g, R_h is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$ or $-I$; and R_i is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, $-I$ or $-C\equiv CH$;

or

C) each R_a, R_b, R_c, R_e, R_k, R_m, R_n, R_o independently is $-R_1$, $-OR_1$, $OCOR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$, $-I$; and each R_g, R_h independently is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$ or $-I$; and R_i is $=O$, $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, $-F$, $-NHR_1$, $-Br$, $-I$ or $-C\equiv CH$;

and

II. Z is defined as follows:

A) Z is X, where X is $>COR_1$, $>\overset{\overset{O}{\|}}{C}-R_1$, $>\overset{\overset{O}{\|}}{C}-OR_1$, $>\overset{OH}{\underset{|}{C}}-R_1$, $>\overset{OH}{\underset{|}{C}}-OR$;

or

B) Z is $=\overset{\underset{R_p}{|}}{C}-X'-$ or $-X'-\overset{\underset{R_p}{|}}{C}=$, where R_p is $-R_1$, $-OR_1$, $-SR_1$, $-F$, $-NHR_2$, $-Br$ or $-I$, and X′ is X, as defined above; or X′ is $=O$;

where, in each formula set forth above, each R_1 and R_2 independently is -H, or substituted or unsubstituted alkyl, alkenyl or alkynl group of 1-6 carbons; and the bond indicated by C•••C is absent or, in combination with the C—C bond is the unit HC=CH.

13. The method of claim 1, wherein said cell-mitosis-inhibiting compound is 2-methoxyestradiol.

14. The method of claim 1, wherein said cell-mitosis-inhibiting compound is 2-fluoroestradiol.

15. The method of claim 1, wherein said cell-mitosis-inhibiting compound is 2-bromoestradiol.

16. The method of claim 1, wherein said cell-mitosis-inhibiting compound is 2-methoxyestrone.

17. The method of claim 1, wherein said cell-mitosis-inhibiting compound is 17-ethynylestradiol.

18. The method of claims 1 or 2 wherein said compound is further characterized in that

A) Z′ is $=\overset{\displaystyle R_n}{\overset{|}{C}}-X'-$ or $-X'-\overset{\displaystyle R_n}{\overset{|}{C}}=$; and

Z" is $-Y-\overset{\displaystyle R_p}{\overset{|}{CH}}-$ or $-\overset{\displaystyle R_p}{\overset{|}{CH}}-Y-$; or

B) Z′ is X; and Z" is $-Y-\overset{\displaystyle R_p}{\overset{|}{CH}}-$ or $-\overset{\displaystyle R_p}{\overset{|}{CH}}-Y-$; or

C) Z′ is $=\overset{\displaystyle R_n}{\overset{|}{C}}-X'-$ or $-X'-\overset{\displaystyle R_n}{\overset{|}{C}}=$; and Z" is Y.

19. The method of claims 3 or 4 wherein said compound is further characterized in that Z is -Y-CH- or -CH-Y-.
   | |
   R_n R_n

20. The method of claims 5 or 6 wherein said compound is further characterized in that Z is =C-X'- or -X'-C=.
 | |
 R_p R_p

21. The compound of claims 7 or 8, wherein said compound is further characterized in that

A) Z' is =C-X'- or -X'-C=; and
 | |
 R_n R_n

Z" is -Y-CH- or -CH-Y-; or
   | |
   R_p R_p

B) Z' is X; and Z" is -Y-CH- or -CH-Y-; or
   | |
   R_p R_p

C) Z' is =C-X'- or -X'-C=; and Z" is Y.
 | |
 R_n R_n

22. The compound of claims 9 or 10, wherein said compound is further characterized in that Z is -Y-CH- or -CH-Y-.
   | |
   R_n R_n

23. The compound of claims 11 or 12, wherein said compound is further characterized in that Z is =C-X'- or -X'-C=.
 | |
 R_p R_p

24. The method of any one of claims 1-6, wherein at least one of R_a-R_p is $-OCH_3$.

25. The compound of any one of claims 7-12, wherein at least one of R_a→R_p is $-OCH_3$.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08767

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/56; C07J 41/00, 31/00, 13/00, 9/00, 5/00, 7/00, 3/00, 1/00.

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/177, 178, 179, 182; 552/516, 522, 523, 524, 525, 535, 536, 540, 541, 542, 543, 544, 548, 549, 550, 551, 552, 553, 554, 555, 557, 558, 559, 560, 562, 563, 564, 565, 566, 567, 569, 571, 572, 573, 575, 582, 583, 584, 585, 599, 603, 604, 605, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 623, 624, 625, 626, 627, 628, 629, 642, 643, 644, 646, 647, 650, 651, 652.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1, 3, 7, 9, and 24, each in part, and claims 13-17; directed to a method of making a medicament compound in which the A ring is aromatic and said compound.

Group II, claims 1, 7, 9, 18, 21, each in part, and 25, directed to a method of making a medicament in which the A ring is aromatic and Z" is Y and Y is O.

Group III, claims 1, 7, 9, 18, 21, each in part, and 25, as in Group II, except that Y is N.

Group IV, claims 1, 3, 7, 18, 21, each in part, and 25, as in Group II, except that the A ring is aromatic and contains 7 carbons and the B ring contains 6 carbon atoms.

Group V, claims 1, 3, 7, 9, 18, 21, each in part, and 25, as in Group IV except that the B ring contains 7 carbon atoms.

Group VI, claims 1 and 18, each in part, in which the A ring contains 6 carbon atoms and the B ring contains 7 carbon atoms.

Group VII, claims 1, 3, 7, 18, 25, each in part, and 25, in which A ring is 7 carbon aromatic and the B ring contains carbons, Z" is Y and Y is O.

Group VIII, claims 1, 3, 7, 18, 21, each in part, and 25, as in
Group VII in which Y is N.

Group IX, claims 2, 4, 8, 10, 18, 21, each in part, and 25, directed to a method of making a medicament in which the A and C rings are each aromatic.

Group X, claims 2, 8, 10, 18, 21, each in part, and 25, directed to a method of making a medicament compound as in Group IX in which the Z" is Y and Y is O.

Group XI, claims 2, 8, 10, 18, 21, each in part, and 25, as in Group IX in which Y is N.

Group XII, claims 2, 8, 18, 21, each in part, and 25, as in Group IX in which the A ring contains 7 carbon atoms.

Group XIII, claims 2 and 18, each in part, as in Group VIII, in which the B ring contains 7 carbon atoms.

Group XIV, claims 2, 18, 25, each in part, and 25 as in Group XII, in which the B ring contains 7 atoms.

Group XV, claims 2, 8, 10, 18, each in part, and 25 in which the B ring has 7 carbons and Y is O.

Group XVI, claims 2, 8, 18, each in part, and 25 in which the B ring has 7 carbons and Y is N.

Group XVII, claims 3 in part, 19, and 24, directed to a method of making a medicament in which there is a keto group at C3, the A ring is aromatic and the B ring contains 6 carbon atoms.

Group XVIII, claims 3 in part and 24, directed to a method of making medicament where the B ring contains 7 carbon atoms.

Group XIX, claims 3 in part and 24, as in Group XVIII, where Z" is Y and Y is O.

Group XX, claims 3 in part and 24, as in Group XVII where Y is N.

Group XXI, claims 4 in part, 19, and 24, directed to making a medicament in which there is a keto group at C-3, the A and C rings are aromatic and the B ring contains 7 carbon atoms.

Group XXII, claims 4 in part, and 24, as in Group XXI, in which Z" is Y and Y is O.

Group XXIII, claims 4 in part, and 24 as in Group XXII, in which Y is N.

Group XXIV, claims 5, 11 in part, and 24, 25, directed to a method of making a medicament which contains one 6-membered aromatic ring.

Group XXV, claims 5, 11 in part, and 20, 23, 24, 25, as in Group XXIV, except that the aromatic ring contains 7 carbon atoms.

Group XXVI, claims 6, 12 in part, and 24, 25 as in Group XXIV, except that the compound contains two 6-membered aromatic rings.

Group XXVII, claims 6, 12 in part, 20, and 24, 25, as in Group XXV except that one aromatic ring contains 7 carbon atoms.

and it considers that the International application does not comply with teh requirements of unity of invention (Rules 13.1, 13.2, and 13.3) for the reasons indicated below:

The international application shall relate to one invention or a group of inventions so linked as to form a single general inventive concept. The first invention of the category first mentioned and the first recited invention of the other categories related thereto have been considered the main invention, PCT Administrative Instructions, Annex B(f)(i), 37 CFR 1.475(d).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08767

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/177, 178, 179, 182; 552/558, 614, 617, 625, 627

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	J. Steroid Biochem., Vol. 32, No. 6, issued 1989, J. Seegers et al., "The Cytotoxic Effects of Estradiol-17beta, catecholestradiols and methoxyestradiols on dividing MCF-7 and HeLa cells" pages 797-809, see entire article.	1, 7, 13 ---------- 14, 15, 16, 17, 24
X -- Y	Chemical Abstracts, Vol. 105, issued 1986, W.J. Wheeler et al., "Mitotic inhibition and aneuploidy induction by naturally occurring and synthetic estrogens in Chinese hamster cells in vitro", see abstract no. 54822, Mutat. Res., 171(1), 1986, 31-41.	1, 17 -------- 13, 14, 15, 16, 24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 OCTOBER 1994	10 NOV 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer REBECCA COOK jd Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08767

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 3, 7, 9, 24 (each in part), 13-17

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

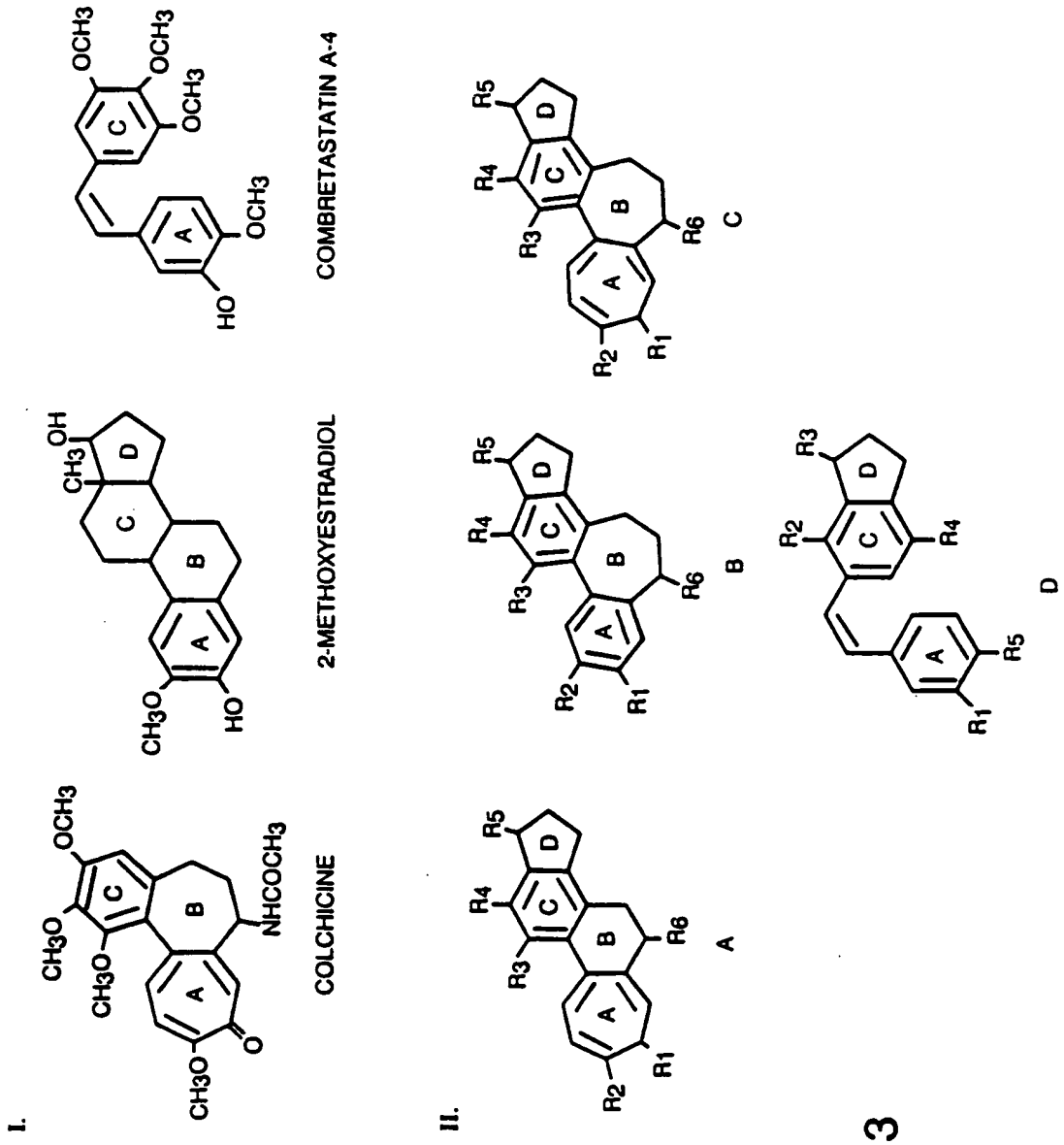
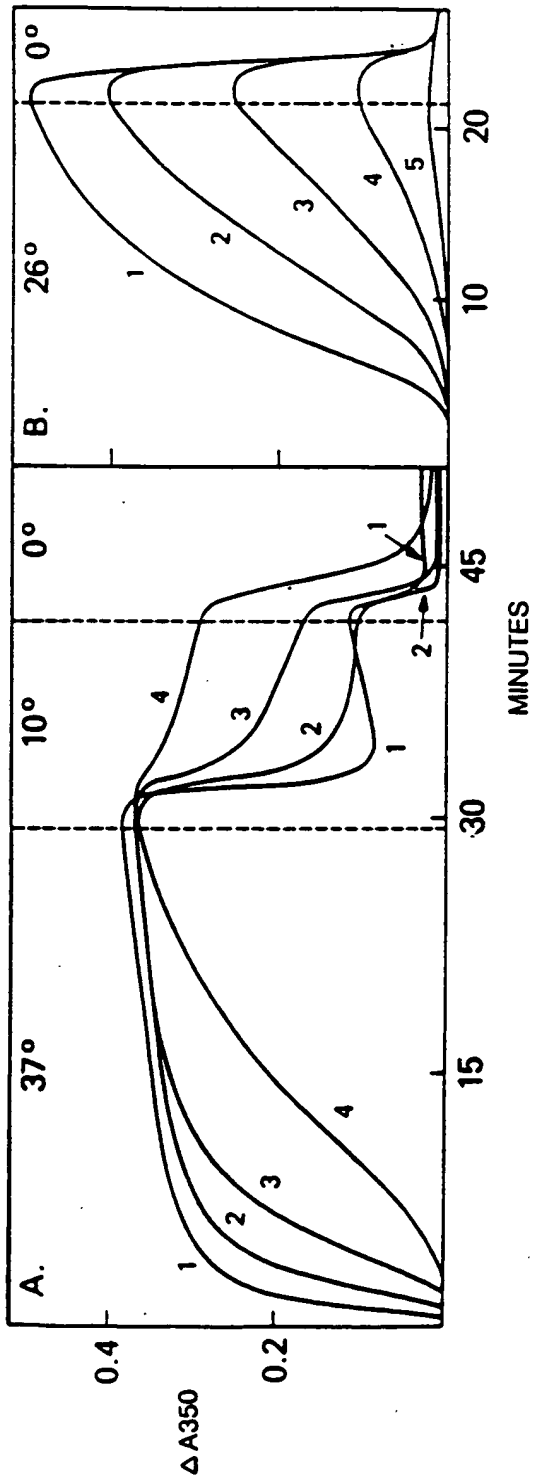

I.
COLCHICINE
2-METHOXYESTRADIOL
COMBRETASTATIN A-4
II.
A
B
C
D

FIG. 3

FIG. 1



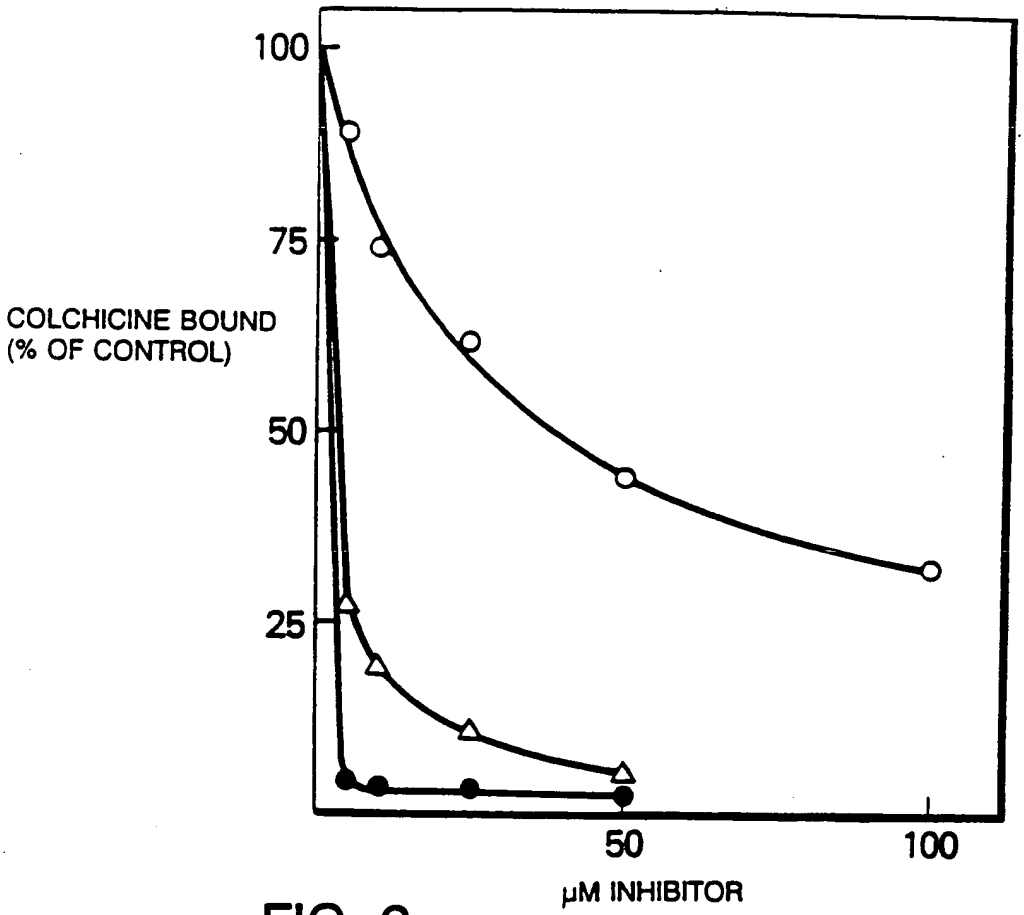


FIG. 2